112. (Once Amended) The composition of claim 66, wherein the polymer is a polymer of amino acids, wherein at least 40% of the amino acids are lysines.

Remarks

The priority claim in the specification has been amended in order to reflect that the parent application, to which priority was previously claimed, itself claimed priority to a U.S. provisional patent application. The priority claim for U.S. patent application serial no. 09/234,358 was of record in that case. Accordingly, no new matter has been added.

Claims 76, 82 and 85 have been deleted. The subject matter of claims 82 and 85 have been introduced into independent claims 55 and 66, respectively.

Claims 55 and 66 have been amended, in part, to include the limitation that the agent is not itself a substrate of transglutaminase. Support for this amendment can be found in previously pending (and now cancelled) claims 82 and 85.

Claims 55 has been further amended, in part, to clarify the meaning of "the linking molecule is not native to the agent". As suggested by the Examiner, the claim has been amended to recite the limitation that "the agent, free of conjugation to the linking molecule, does not contain the linking molecule". This is not a narrowing amendment.

Claims 67, 111 and 112 have been amended to clarify their meaning at the Examiner's suggestion. These are not narrowing amendments.

Claims 71, 74, 75, 81 and 88 have been amended in order to correct claim dependency.

Claims 86, 89, 92, 95 and 98 have been amended to clarify their meaning at the Examiner's suggestion. These are not narrowing amendments.

Claims 102 and 103 have been amended to reflect that the agent is in the microparticle. Support for these amendments can be found on page 8, line 17, and page 14, line 23.

No new matter has been added.

Claims 55, 57, 66, 67, 71 and 74, 75, 77-112 are currently pending.

Applicants reserve the right to pursue the full breadth of the subject matter of originally filed claims 53 and 65 in a continuing application.

The Claimed Invention

The claimed invention relates, in part, to compositions comprising conjugates of active agents and linking molecules, that can be applied to a body tissue using transglutaminase. The active agents are nonextracellular matrix protein, nonlabeling agents and can include chemical agents such as

pharmaceutical agents, sunscreen agents, ligands and/or receptors of ligand-receptor pairs, insecticides, and repellants; enzymes such as cholinesterase and phosphodiesterase; and non-protein agents. The active agents of the pending claims are not substrates of transglutaminase, yet they are conjugated to linking molecules that are substrates of transglutaminase. The linking molecule, in turn, is not native to the agent (i.e., the agent, when free of conjugation, does not contain the linking molecule). The linking molecules are either carboxamide-bearing molecules comprising at least two contiguous linked glutamines, or polymers that comprise at least three contiguous lysines. The linking molecules in their broadest sense may contain non-amino acid units, provided they contain at least two linked glutamines or at least three contiguous lysines. Additionally, the linking molecules can be rich in carboxamides and aliphatic amines, such as molecules that include at least three linked carboxamides or aliphatic amines, or polymers that contain at least 20% carboxamides (e.g., glutamines) or 20% aliphatic amines (e.g., lysines).

The claimed invention also relates, in part, to kits that comprise the above described conjugates in a first container, and transglutaminase in a second container. The kits can optionally further comprise in another container an additional linking molecule that can be used, for example, to render the body tissue more receptive to interaction with the conjugate of the kit.

Claim Objections

Claims 71, 74-76, 81 and 86-93 are objected to because the claims depend on now cancelled claims 53 or 65. Claim 76 has been cancelled, for reasons set forth below. Claims 71, 74, 75, 81 and 88 have been amended to depend from pending claims 55 or 66. The claim dependency of these claims and those that depend therefrom should now be correct.

Rejections under 35 U.S.C. 112, first paragraph

Claims 102 and 103 are rejected under 35 U.S.C. 112, first paragraph, because according to the Examiner, "the specification fails to support the conjugate being in or on a microparticle." Applicants have amended claims 102 and 103 to reflect that the agent is in a microparticle. Support for these amendments can be found on page 8, line 17, and page 14, line 23.

In view of these amendments, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 102 and 103 under 35 U.S.C. 112, first paragraph.

Rejections under 35 U.S.C. 112, second paragraph

Claims 55, 57, 67, 71, 74-81, 82, 85-93, 95, 97-99, 104-108, 111 and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71, 74-76, 81 and 86-93 are rejected as being "confusing and unclear by depending on canceled claims 53 or 65." Applicants have amended claims 71, 74-76, 81 and 88 to reflect proper claim dependency. Remaining claims 86, 87 and 89-93 should now also reflect proper claim dependency.

Claim 76 is rejected as being "uncertain as to meaning in scope" in the recitation of "a polymer rich in glutamine" because, according to the Examiner, "while the specification may define this limitation as having at least 20% glutamine, the term in the claims can have other meanings, and the claims rather than the specification define the metes and bounds of the invention." For the record, Applicants respectfully traverse the Examiner's assertion that "polymer rich in glutamine" can have other meanings when the specification clearly defines a polymer rich in glutamine as a molecule wherein at least 20% of the units of the polymer carry a carboxamide in the form of glutamine, or wherein the molecule includes at least 3, preferably 4 and most preferably 5 separate and discretely spaced by a regular distance carboxamides in the form of contiguous, linked glutamines". (See page 11, lines 18-26.) Respectfully, the patent applicant is judicially-sanctioned to be his or her own lexicographer, and the specification can be referred to in order to construe a claim term. Regardless, Applicants have cancelled claim 76 in view of other the scope of other pending claims (specifically claims 55, 57 and 104), which embrace all aspects of the meaning of "a polymer rich in glutamine". Cancellation of claim 76 does not represent surrender of it subject matter, as this subject matter is embraced by still pending claims 55, 57 and 104.

Claims 67, 111 and 112 are rejected as being "confusing by requiring the polymer of claim 66 to comprise amino acids since claim 66 requires the polymer to contain amino acids." Applicants have amended claims 67, 111 and 112 at the Examiner's suggestion.

Claims 86, 89, 92, 95 and 98 are rejected as being unclear. Applicants have amended these claims per the Examiner's suggestion. These are not narrowing amendments.

Claim 55 and claims dependent thereon are rejected as being "confusing and unclear by (the recitation of the) 'linking molecule is not native to the agent'". Applicants have amended the claim to recite that the agent, free of conjugation to the linking molecule, does not contain the linking molecule. This is not a narrowing amendment.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 55, 57, 67, 71, 74, 75, 77-81, 82, 85-93, 95, 97-99, 104-108, 111 and 112 under 35 U.S.C. 112, second paragraph.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 55, 57, 66, 67, 71 and 74-112 under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (5,490,980), in view of Kahlem et al. (Reference CD), Greenberg et al. (Reference CF) and Davies et al. (Reference CA), and if necessary in further view of Green et al. (USP 5,525,336). The bases of the Examiner's rejection and the Applicants' rebuttal (including the teaching of the prior art references) were discussed in the Office Action Response dated March 5, 2001. The claimed invention has been described above.

As a result of the telephone interview with the Examiner, Applicants amended claims 55 and 66 to recite the limitation that the active agent is not itself a substrate of transglutaminase, thereby incorporating the limitations of then pending and now cancelled claims 82 and 85 into claims 55 and 66 respectively.

Applicants believe that the combination of references do not render obvious the pending claims for at least the same reasons set forth in the earlier Office Action Response, and also because the references teach the linking of proteins to other proteins, all of which naturally are substrates of transglutaminase (as discussed in the telephone interview). In contrast, the present claims relate to the modification of agents that naturally are not substrates of transglutaminase, by conjugation to linking molecules that are substrates of transglutaminase.

Applicants reiterate the deficiencies in the teachings of the primary reference as applied to the now amended claims. The primary reference, Richardson et al., does not teach (1) modification of an active agent, including a non-protein active agent, by the addition of carboxamide groups such as glutamines (claim 55 and claims dependent thereon); (2) modification of an active agent by addition of contiguous lysines (claim 66 and claims dependent thereon); (3) modification of an active agent by addition of polymers rich in glutamine or lysine (claims 57, 67, 75 and 104-112); (4) modification of an active agent by addition of carboxamide-carrying or aliphatic amine-carrying polymers (claims 55, 66 and 74); (5) modification of the active agent by addition of contiguous carboxamides or aliphatic amines (claims 55, 66 and 74); and (7) modification of active agents that are enzymes (claims 55, 66, 99 and 100).

The secondary references do not supply the deficiencies of Richardson et al. Greenberg et al., Davies et al., and Green et al. repeatedly teach that transglutaminase has a broad specificity for lysine substrates yet a very restricted specificity for glutamine substrates. The references further teach that the presence of glutamines in a peptide or protein bound form is a necessary but not sufficient condition for rendering such glutamines substrates of transglutaminase. None of the secondary references teaches modification of active agents, particularly non-protein active agents, by addition of glutamines or lysines. Rather, as discussed in the telephone interview, the secondary references simply characterize the activity

of transglutaminases upon naturally occurring protein substrates of transglutaminase. In view of the teachings of Greenberg et al., Davies et al., and Green et al., one of ordinary skill in the art would not choose to modify active agents with carboxamide groups, particularly when those active agents are not protein in nature. Only the present invention teaches the modification of active agents including nonprotein active agents by the addition of carboxamide-carrying linking molecules as transglutaminase substrates.

The Kahlem et al. reference reports the involvement of polyglutamine containing peptides in the progression of neurodegenerative diseases. The reference reports that polyglutamines ranging in length from 2 to 18 residues can act as amine acceptors in a transglutaminase catalyzed reaction if flanked on both the amino and carboxy ends with amino sequence from SCA1 associated proteins (i.e., within the context of a peptide or protein). The reference does not suggest that such polyglutamine containing peptides have utility in the drug delivery formulations. This is significant since two of the authors of the Kahlem et al. reference are co-inventors of the present invention. These co-authors were focused on the impact of naturally occurring polyglutamines in the body, and their role in the progression of certain neurodegenerative diseases, and did not recognize that polyglutamines could be used in the delivery of active agents to subjects.

By combining the Richardson et al. reference with Kahlem et al., the Examiner is engaging in impermissible hindsight. In the absence of the present invention, there is nothing in either the Richardson et al. or the Kahlem et al. reference to motivate one of ordinary skill in the art of drug delivery to look to the Kahlem et al. reference as providing a teaching relevant to that field, since the Kahlem et al. reference relates to mechanisms of neurodegenerative disease while Richardson et al. relates to agent delivery for cosmetic and therapeutic purposes. Accordingly, one of ordinary skill in the art would not look to the Kahlem et al. reference for guidance on how to modify the teachings of Richardson et al., especially because the Kahlem et al. authors (who are inventors of the instant application) failed to make such a connection.

In view of the amendments to claims 55 and 66 and the foregoing arguments, Applicants respectfully request that the Examiner reconsider and withdrawn the rejection under 35 U.S.C. §103(a).

Summary

Applicants believe that each of the pending claims now is in condition for allowance. Applicants respectfully request that the Examiner telephone Applicants' representative in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' representative would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 266).

Respectfully submitted,

Maria A. Trevisan, Reg. No. 48,207
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210-2211
Attorneys for Applicant(s)
Tel. no. (617) 720-3500

ATTORNEY'S DOCKET NO.: H0535/7009 (ERG/MAT)
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APPENDIX A:
MARKED-UP CLAIMS

55. (Twice Amended) A composition of matter comprising:

a conjugate of a nonextracellular matrix protein, nonlabeling agent and a carboxamide-carrying linking molecule,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellant and a component of a high affinity noncovalent coupling pair,

wherein the agent is not itself a substrate of transglutaminase,

wherein [the linking molecule is not native to] the agent, free of conjugation to the linking molecule, does not contain the linking molecule, and

wherein the linking molecule comprises at least two contiguous linked glutamines, and is a substrate of transglutaminase.

57. (Once Amended) The composition of claim 55, wherein the linking molecule comprises a polymer of amino acids containing at least 20% glutamines.

66. (Twice Amended) A composition of matter comprising:

a conjugate of a nonextracellular matrix protein, nonlabeling agent and a polymer,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, an insect repellant and a component of a high affinity noncovalent coupling pair,

wherein the agent is not itself a substrate of transglutaminase, and

wherein the polymer comprises at least 3 contiguous lysines attached to one another by peptide bonds, and is a substrate of transglutaminase.

67. (Twice Amended) The composition of claim 66, wherein the polymer [comprises] is a polymer of amino acids, [and] wherein at least 20% of the amino acids are lysines.

71. (Twice Amended) A kit comprising

a package housing:

a first container containing the composition of claim [53] 55 and

a second container containing transglutaminase.

74. (Once Amended) The composition of claim [53] 55, wherein the linking molecule comprises at least 5 linked units, each unit being a carboxamide-bearing substrate for transglutaminase.

75. (Once Amended) The composition of claim [53] 55, wherein the linking molecule is 4 or more contiguous glutamines attached directly to one another by peptide bonds.

77. (Once Amended) The composition of claim 55, wherein the component of a high affinity noncovalent binding pair is selected from the group consisting of a ligand of a ligand-receptor complex, and a receptor of a ligand-receptor complex.

78. (Once Amended) The composition of claim 55, wherein the agent is selected from the group consisting of a cholinesterase and a phosphodiesterase.

79. (Once Amended) The composition of claim 55, wherein the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

80. (Once Amended) The composition of claim 55, wherein the agent is a pharmaceutical agent and the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

81. (Once Amended) The composition of claim [53] 55, wherein the agent is a nonprotein.

83. (Once Amended) The composition of claim 66, wherein the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

84. (Once Amended) The composition of claim 66, wherein the agent is a nonprotein.

86. (Once Amended) The kit of claim 71, further comprising

a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently [attached] attaching to the composition

contained in the first container [if] in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

87. The kit of claim 71, further comprising calcium housed by said package, except that said calcium is not in said second container.

88. (Once Amended) A kit comprising

a package housing:

a first container containing the composition of claim [65] 66, and

a second container containing transglutaminase.

89. (Once Amended) The kit of claim 88, further comprising

a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently [attached] attaching to the composition contained in the first container [if] in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

90. The kit of claim 88, further comprising calcium housed by said package, except that said calcium is not in said second container.

91. (Once Amended) A kit comprising

a package housing:

a first container containing the composition of claim 81, and

a second container containing transglutaminase.

92. (Once Amended) The kit of claim 91, further comprising

a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently [attached] attaching to the composition contained in the first container [if] in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

93. The kit of claim 91, further comprising calcium housed by said package, except that said calcium is not in said second container.

94. (Once Amended) A kit comprising

a package housing:

a first container containing the composition of claim 84, and

a second container containing transglutaminase.

95. (Once Amended) The kit of claim 94, further comprising

a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently [attached] attaching to the composition contained in the first container [if] in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

96. The kit of claim 94, further comprising calcium housed by said package, except that said calcium is not in said second container.

97. (Once Amended) A kit comprising

a package housing:

a first container containing the composition of claim 102, and

a second container containing transglutaminase.

98. (Once Amended) The kit of claim 97, further comprising

a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently [attached] attaching to the composition contained in the first container [if] in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

99. The composition of claim 55, wherein the agent is an enzyme.

100. The composition of claim 66, wherein the agent is an enzyme.

101. The composition of claim 100, wherein the enzyme is selected from the group consisting of a cholinesterase and a phosphodiesterase.

102. (Once Amended) The composition of claim 55, wherein the [conjugate] agent is in [or on] a microparticle.

103. (Once Amended) The composition of claim 66, wherein the [conjugate] agent is in [or on] a microparticle.

104. The composition of claim 55, wherein the linking molecule comprises at least three contiguous linked glutamines.

105. The composition of claim 55, wherein the linking molecule comprises at least four contiguous linked glutamines.

106. The composition of claim 55, wherein the linking molecule comprises at least five contiguous linked glutamines.

107. The composition of claim 55, wherein the linking molecule comprises a polymer of amino acids containing at least 30% glutamines.

108. The composition of claim 55, wherein the linking molecule comprises a polymer of amino acids containing at least 40% glutamines.

109. The composition of claim 66, wherein the polymer comprises at least 4 contiguous lysines attached to one another by peptide bonds.

110. The composition of claim 66, wherein the polymer comprises at least 5 contiguous lysines attached to one another by peptide bonds.

111. (Once Amended) The composition of claim 66, wherein the polymer [comprises] is a polymer of amino acids, [and] wherein at least 30% of the amino acids are lysines.

112. (Once Amended) The composition of claim 66, wherein the polymer [comprises] is a polymer of amino acids, [and] wherein at least 40% of the amino acids are lysines.

MARKED-UP SPECIFICATION

Please re-write the paragraph beginning on page 1, line7, as follows:

This application is a continuation-in-part of U.S. patent application serial no. 09/234,358, filed January 20, 1999, entitled "Transglutaminase Linkage of Agents to Tissue" which is pending, and which claims priority to U.S. provisional patent application serial no. 60/071,908, filed January 20, 1998, entitled "Transglutaminase Linkage of Agents to Tissue" which is now abandoned. This entire reference is incorporated herein.